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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,460	08/19/1998	HERMAN WALDMANN	1283-36	7809

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	32

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/125,460	WALDMANN ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,26-29,31-69 and 71-75* is/are pending in the application.

4a) Of the above claim(s) *18,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-29,31-69 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 30 and 70 have been canceled.

Claims 26 and 64 have been amended.

Claims 73-75 have been added.

2. Claims 18, 71-72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in Paper No. 28.

3. Claims 26-29, 31-69 and 73-75 are under examination.

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejection.

Rejections Withdrawn

6. The rejection of claims 26-70 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims and arguments.

7. The rejection of claims 26, 31-32, 54-57, 63-65 under 35 U.S.C. 102(b) as being anticipated by Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5) is withdrawn in view of the amendments to the claims.

Response to Arguments

8. The rejection of claim 59 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is maintained.

The response filed 5/12/03 has been carefully considured but is deemed not to be persuasive. The response states that the term "Campath-1" refers to a series of monoclonal antibodies and the antibody has been described by Riechmann et al (Nature 332:323, 1988) and the full sequence of the humanized antibody is available at a recited web address (see page 8 of response). In response to this argument, the response states that there are a series of antibodies and as such it is not clear which one is being claimed. In addition, Riechmann sequence is only the heavy and light chain and not the entire antibody sequence and Riechmann's antibody is directed only to one specific humanized CAMPATH-1 antibody, namely the rat IgG2a YTH34.5HL antibody. The claim is not limited to this particular rat humanized CAMPATH-1 antibody. With regard to the web site the examiner could not obtain a sequence and in addition if a sequence was obtained the claim is not limited to any particular CAMPATH-1 antibody. Applicant is invited to clarify the scope of the humanized CAMPATH-1 antibody set forth in claim 59 and address the biological deposit issues.

9. The rejection of claims 26-29, 31-69 and newly submitted claims 73-75 under 35 U.S.C. 103(a) as being unpatentable over Isaacs et al (Therapeutic Immunology 1:303-312, 1994, IDS #5) and further in view of Carter et al (U.S. Patent 6,054,297, CON to 1992) and Riechmann et al (Nature 332:323, 1988, IDS #5) is maintained.

The response filed 5/12/03 has been carefully considured but is deemed not to be persuasive. The response states that none of the references suggest modification of a therapeutic antibody to effect removal of binding ability, rather all of the references teach modification such that binding is maximized and in fact Isaacs teach away from the use of non-cell binding , non-mixed molecule variants as a means of inducing tolerance (see page 310, column 1) (see page 12 of response). In response to this argument, Isaacs clearly teach the importance of non-cell binding antibodies and in contrast to applicant's assertions, the indication of no special advantage by Isaacs et al was limited to a particular case of CBA.ca mice receiving the therapeutic antibody YTS 169.4 (also see page 310, column 1). Applicants comments on mixed molecules and non-mixed molecule variants are acknowledged.

Applicant's assertions are in contrast with the clear teaching of Isaacs and Waldmann (H. Waldmann being a coinventor of the instant application), which is drawn to non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies (see entire document, including the Abstract).

For example this reference concludes (page 311, column 2, paragraph 2) by stating that:

Based upon a demonstration of T cell dependency of the anti-Ig response; we have devised regimes for inducing tolerance to cell-binding therapeutic mAbs. These are one- or two-step processes depending upon the characteristics of the therapeutic agent and these regimes might eventually be applied to the clinical situation. Our conclusions also suggest that some patients will be naturally tolerant of the at least some chimeric or humanized mAbs, and remain immunologically unresponsive upon repeated dosing.

One of ordinary skill in the art at the time the invention was made would have been motivated to select non-cell binding antibody variants, including fragments, of therapeutic antibodies, including the CAMPATH-1 antibody, to generate therapeutic unresponsiveness to clinically useful antibodies by a variety of recombinant means available to the ordinary artisan at the time the invention was made, as evidenced by Carter et al. In addition, it is well known that the CDR residues influence binding and Carter et al even teach that one can reduce affinity in some circumstances and in view of Isaacs et al who tech non-binding variants, it would have been obvious to alter the CDR residues as taught by Carter. Therefore the claimed limitations encompassing substitutions and alterations in sequences as well as reduced affinity would have been expected properties of selecting for non-cell binding variants of therapeutic antibodies at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie

obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703)

306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879